

UNSOLICITED REVIEW

NLRP3 inflammasome: A likely target for the treatment of allergic diseases

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Summary

Allergic diseases, such as asthma, rhinitis, dermatitis, conjunctivitis, and anaphylaxis, have recently become a global public health concern. According to previous studies, the NLRP3 inflammasome is a multi-protein complex known to be associated with many inflammatory conditions. In response to allergens or allergen/damage-associated molecular signals, NLRP3 changes its conformation to allow the assembly of the NLRP3 inflammasome complex and activates caspase-1, which is an evolutionarily conserved enzyme that proteolytically cleaves other proteins, such as the precursors of the inflammatory cytokines IL-1 β and IL-18. Subsequently, active caspase-1 cleaves pro-IL-1 and pro-IL-18. Recently, accumulating human and mouse experimental evidence has demonstrated that the NLRP3 inflammasome, IL-1 β , and IL-18 are critically involved in the development of allergic diseases. Furthermore, the application of specific NLRP3 inflammasome inhibitors has been demonstrated in animal models. Therefore, these inhibitors may represent potential therapeutic methods for the management of clinical allergic disorders. This review summarizes findings related to the NLRP3 inflammasome and its related factors and concludes that specific NLRP3 inflammasome inhibitors may be potential therapeutic agents for allergic diseases.

1 | INTRODUCTION

Allergic diseases have become a major world-wide public health concern over recent decades.^{1,2} Between 20% and 30% of inhabitants in Western countries suffer from at least one type of allergic disease.³ Allergic diseases include several conditions caused by hypersensitivity of the immune system that usually triggers a pathological reaction. The most prevalent allergic diseases include allergic asthma, allergic rhinitis, allergic dermatitis, allergic conjunctivitis, eczema, and anaphylaxis. Clinical manifestations characterized by allergic hypersensitivity suggest that both genes and environmental factors contribute to allergic diseases.⁴ This review summarizes the role of the NLRP3 inflammasome and its downstream factors in some allergic diseases.

Pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) are sensed by components of the

innate immune system.⁵ Innate immune cells express pattern recognition receptors (PRRs) that can identify endogenous and exogenous PAMPs or DAMPs.⁶ The currently known PRRs include Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs). TLRs are located both in the cell compartment and on the cell membrane, while NLRs are located in the cytosol. The various subfamilies of the NLR family are distinguished by their N-terminal effector domains, including the acidic transactivation domain, the pyrin domain (PYD), the caspase recruitment domain (CARD), and baculoviral inhibitory repeat-like domains.^{7,8} The central nucleotide-binding oligomerization domain, which is a C-terminal leucine-rich repeat domain, is a common feature of all NLR proteins.⁹ The NLR family of proteins plays an important role in perceiving inflammatory stimuli and subsequently mediating inflammasome assembly. Nod-like receptor family pyrin domain-containing proteins (NLRPs) are among the most important subfamilies of NLR family proteins. The activation of some NLRPs leads to the formation of a large multimolecular signalling

Xiao and Xu contributed equally to this work.

platform consisting of an active NLRP, a bipartite adaptor protein, caspase-1, and the inflammasome adaptor protein apoptosis-associated speck-like protein containing CARD (ASC).¹⁰ Yasunori Fujita et al¹¹ first identified NLRP3 in 2001, and NLRP3 is currently considered the innate immune regulatory complex that activates caspase-1 to generate IL-1 β and IL-18 upon activation by various signals.

2 | NLRP3 INFLAMMASOME

The inflammasome is a complex of inflammatory proteins that can identify pathogens in the development of inherent immunity. Recent research has shown that inflammasomes have a substantial impact on inflammation. Several inflammasomes, including NLRP1, NLRP3, NLRC4, and NLRP6, have been studied thus far.¹² The NLR family pyrin domain containing 3 (NLRP3) is relevant for several human allergic disorders because its activation is associated with a range of allergic stimuli, such as silica, alum, and other allergens.^{5,13,14}

The NLRP3 inflammasome is a high molecular weight protein complex that includes interactions among NLRP3, ASC, and Caspase-1 (Figure 1). NLRP3, which is encoded by cold-induced autoinflammatory syndrome gene (CIAS-1), is also known as cryopyrin, PYPAF1, and Nalp3 and is an NLR family member that contains an N-terminal PYD, a central NACHT and a C-terminal LRR domain.¹⁵ Specifically, NLRP3 is characterized by its N-terminal PYD, which allows NLRP3 to recruit ASC through PYD-PYD interactions, thus facilitating the recruitment of procaspase-1 to form inflammasome complexes.^{16,17} Caspase-1 is

the most fully characterized proinflammatory caspase and is synthesized as an inactive zymogen.¹⁵ ASC, which is encoded by Pycard, is an adaptor protein that interacts with NLRP3 and caspase-1 through its PYD domain and CARD domain, respectively. In resting monocytes and macrophages, inflammatory stimuli can induce ASC redistribution in the cytosol to activate the NLRP3 inflammasome, which processes pro-IL-1 β and pro-IL-18.^{18–20} Macrophages and monocytes produce pro-IL-1 β and pro-IL-18 and then activate caspase-1.

Activated caspase-1 processes pro-IL-1 β and pro-IL-18 into their mature active forms, which are then secreted into the extracellular space to perform their immune functions.²¹ Studies have shown that IL-18 and IL-1 β secretion and cell death are dependent on the activation of several inflammasomes, including NLRP3.²² IL-1 β is also known as a proinflammatory response cytokine and is mainly secreted by mononuclear macrophage cells. IL-1 β can promote the differentiation of Th17 cells, maintain the production of Th17-associated cytokines, and facilitate allergic responses.^{23,24} IL-18 can stimulate mast cells, T cells, and basophils to secrete Th2 cytokines, such as IL-13 and IL-4. IL-18 can also enhance Th2 and Th1 cell-mediated immune responses.^{25,26} Thus, NLRP3 is an important PRR within the cytoplasm. Moreover, caspase-1 is a converting enzyme that catalyses IL-1 β and IL-18 into their mature forms and is an inflammatory effector protein of the NLRP3 inflammasome. However, the molecular mechanism that triggers inflammasome assembly is still unclear. To date, the reported mechanisms include the following 3 classical models (Figure 2): changes in K⁺ influx/efflux from the cell, Ca²⁺ signalling-induced lysosome damage, and production of reactive oxygen species (ROS).¹⁹ First, K⁺ efflux is induced in

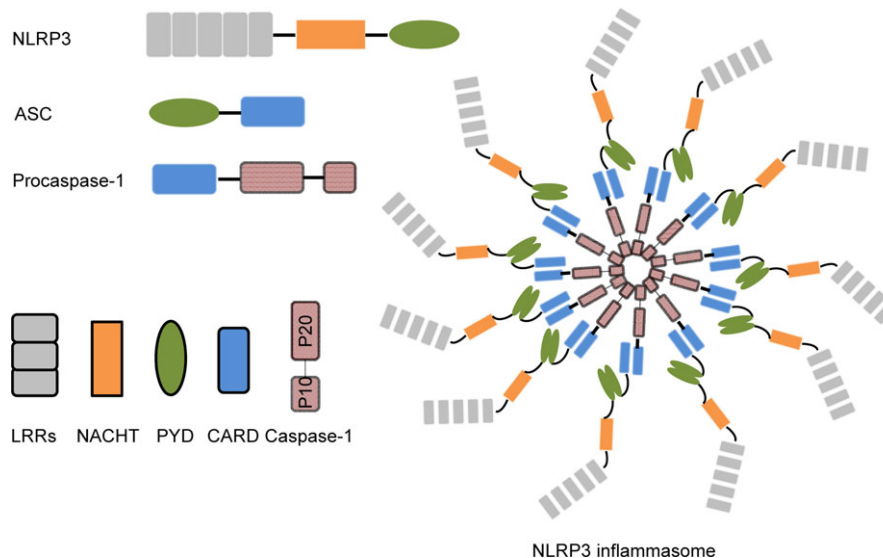


FIGURE 1 Composition of the NLRP3 inflammasome. NLRP3 contains an N-terminal PYD, central NACHT, and C-terminal LRR. ASC comprises an N-terminal PYD and C-terminal CARD and is an adaptor protein that bridges NLRP3 and caspase-1. ASC interacts with NLRP3 through its PYD and caspase-1 through its CARD. NLRP3 is marked by an N-terminal PYD, which allows NLRP3 to recruit ASC through PYD-PYD interactions, thus facilitating the recruitment of procaspase-1 to form NLRP3 inflammasome complexes. ASC, inflammasome adaptor protein apoptosis-associated speck-like protein containing CARD; CARD, cysteinyl aspartate-specific proteinase (caspase) recruitment domain; LRR, leucine-rich repeat domain; NACHT, nucleotide-binding oligomerization domain; NLRP3, NOD-like receptor family pyrin domain containing 3; PYD, pyrin domain

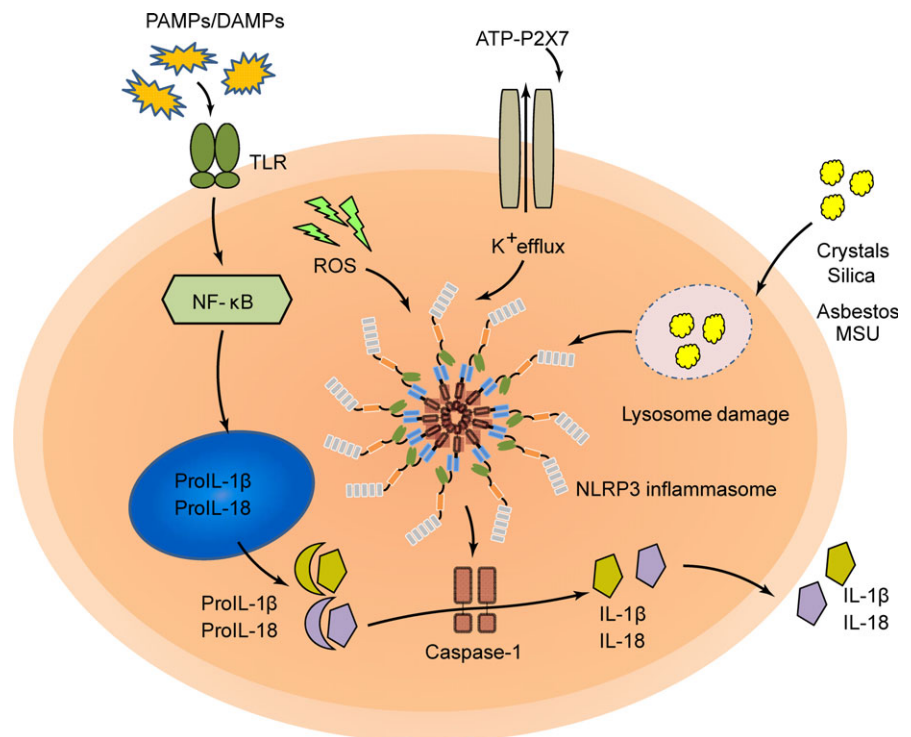
response to NLRP3 stimuli, such as ATP, nigericin, and particulate matter, and the cytosolic K^+ concentration has been proposed to be a common trigger of NLRP3 inflammasome activation; however, an increase in intracellular Na^+ is not necessary. Pétrilli et al provided evidence that the activation of NALP3 is blocked by the inhibition of K^+ efflux from cells. These authors also found that a decrease in cytosolic K^+ is necessary and sufficient for caspase-1 activation.^{27,28} Piccini et al²⁹ found that P2X7 receptor-dependent pore formation in response to extracellular ATP and K^+ efflux allows extracellular PAMP and/or DAMP to access the cytosol and directly activate NLRP3. Second, when crystalline agonists, such as silica and asbestos, are engulfed by cells, phagosomes are destroyed by lysosomal damage and release their contents into the cytosol, which can then be recognized by NLRP3 and cause NLRP3 inflammasome activation.³⁰ Third, ROS production is a crucial upstream event of inflammasome assembly. Dostert et al reported that silica crystals stimulate ROS to induce the activation of NLRP3 in human PBMCs. Zhou et al also found that the application of ROS chemical inhibitors causes mitochondrial dysfunction in NLRP3 activation and, therefore, attenuates inflammatory symptoms.^{31,32} Further research has revealed that ROS production is induced by thioredoxin and the thioredoxin-interacting protein (TXNIP) complex, resulting in the dissociation of the complex and subsequent binding to NLRP3, which leads to NLRP3 activation and ASC and procaspase-1 recruitment.^{15,33} Mitochondrial ROS induces the translocation of CLICs and is believed to be an essential and proximal upstream event of NLRP3 activation.³⁴

3 | ROLES OF NLRP3 INFLAMMASOMES, IL-1 β AND IL-18 IN ASTHMA

NLRP3 has been shown to participate in the pathogenesis of many diseases, including allergic reactions, autoimmune diseases, and metabolic diseases (Table 1). Furthermore, a recent report demonstrated that NLRP3 combines with and transactivates the IL4 promoter to bind transcription factor IRF4. Thus, NLRP3 promotes Th2 cells and asthma-like symptoms. NLRP3 deficiency affects the Th2 differentiation process, revealing that NLRP3 may function as a Th2 transcription factor that is required for the Th2-dependent allergic response.³³

Asthma is a frequent chronic inflammatory respiratory disease with airway hyperreactivity associated with innate lymphoid cells, mast cells, eosinophils and T lymphocytes. People who are susceptible to such inflammation can suffer from recurrent wheezing attacks, shortness of breath, chest tightness, coughing, and other symptoms. Mouse models of asthma classically involve sensitization to and challenges with various protein antigens, such as ovalbumin (OVA), or the inhalation of aeroallergens, such as house dust mite (HDM) antigens.³⁵ T lymphocytes, particularly Th2 cells and Th2-type cytokines, are considered the immunological signatures of allergic immune responses to intruding antigens.³⁶ Recent studies have demonstrated that asthma can no longer be simply regarded as a disease of the adaptive immune system and should be considered a crosstalk between the innate and adaptive immune systems, both of which play crucial roles in the initiation and propagation of allergic immune responses.³⁶

FIGURE 2 Activation of the NLRP3 inflammasome. Extracellular and intracellular PAMPs or DAMPs are recognized by TLRs, which results in the transcription of pro-IL-1 β and pro-IL-18 through NF- κ B signalling. NLRP3 is induced by K^+ efflux, lysosome damage, or ROS production, causing NLRP3 inflammasome complex assembly and the subsequent release of active caspase-1. Active caspase-1 cleaves pro-IL-1 β and pro-IL-18 into their mature forms, which are then secreted extracellularly. ATP, adenosine triphosphate; DAMP, danger-associated molecular pattern; IL, interleukin; NLRP3, NOD-like receptor family pyrin domain containing 3; PAMP, pathogen-associated molecular pattern; ROS, reactive oxygen species; TLR, Toll-like receptor



4 | ROLE OF IL-1B IN ASTHMA

Accumulating evidence suggests that IL-1 and IL-18 are involved in the development of asthma and pulmonary Th2 immune responses.³⁷ Many studies have shown that the IL-1 β levels in the bronchoalveolar lavage fluid (BALF),³⁸ sputum,³⁹ and serum⁴⁰ of patients with symptoms were higher than those in controls. Furthermore, Sousa et al found that the expression of both IL-1 β and IL-1 receptor antagonist (IL-1Ra) is increased in asthmatic bronchial epithelium. Additionally, the percentage of macrophages producing IL-1 β was significantly increased in asthmatic submucosa.⁴¹ Under normal conditions, the actions of IL-1 are balanced by IL-1Ra and other natural IL-1 inhibitors.⁴² The intratracheal administration of active human IL-1 β to mice can induce airway inflammation and tissue remodelling⁴³; however, the airway hypersensitivity responses dramatically decreased in response to the introduction of recombinant human IL-1Ra in a murine model of asthma before the allergen challenge.⁴⁴ In the OVA model, asthma was dependent on IL-1 based on data obtained from gene-deficient mice.⁴⁵ IL1R1 (interleukin 1 receptor type 1) dependence was further found in the innate response to the protease allergen papain.⁴⁶ Another study using a murine model of asthma reported that genetic disruption of the IL-1 signalling pathway could strongly attenuate the allergic response.⁴⁷

5 | ROLE OF IL-18 IN ASTHMA

The involvement of IL-18 in the pathogenesis of asthma has also been observed in some studies. IL-18 was increased in the plasma,⁴⁸ lung tissue⁴⁸ and sputum⁴⁹ of asthmatic patients compared with that in healthy subjects. Another study observed that compared with healthy subjects, the IL-18 concentrations in nasal washings after an allergen challenge and basophil proportions were higher in occupational asthma patients.⁵⁰ Additionally, Imaoka et al identified that the serum IL-18 levels in asthmatic subjects were significantly higher than those in other groups and that the IL-18 protein levels were remarkably over-expressed in the airway epithelium and smooth muscle cells in airway biopsies of allergic asthmatic subjects.⁵¹ Sawada et al⁵² found that IL-18 overexpression in the lungs increased type 1 and type 2 cytokines in an ovalbumin induction mouse model to promote airway hyperresponsiveness. Similarly, Campbell et al⁵³ assayed IL-18 in whole-lung homogenates and found that compared with nonallergic mice, the baseline IL-18 levels were significantly higher in the allergic mice. Kumano et al showed enhanced eosinophil recruitment following the administration of recombinant IL-18 into the BALF and trachea of allergic OVA-immunized mice. In a mouse asthma model induced by OVA, significantly higher numbers of neutrophils were observed in the BALF, while pretreatment with IL-1Ra or anti-IL-18 markedly decreased the neutrophil influx.⁵⁴ These findings suggest that IL-1 and IL-18 contribute to the development and exacerbation of asthma airway inflammation.⁵⁵

6 | ROLE OF CASPASE-1 IN ASTHMA

Caspase-1 was the first member of the caspase family shown to convert pro-IL-1 β into its mature form. Grzegorzczuk et al⁵⁶ found that the mean caspase-1 concentration in the serum of allergic patients was significantly higher than that in the non-atopic group, and a significant relationship was observed between the caspase-1 levels and baseline apoptosis of mononuclear cells only in the atopic asthmatic patients. Another study showed that OVA-sensitized mice treated with a caspase inhibitor before a challenge had a marked reduction in inflammatory cell infiltration, pulmonary blood vessels, and Th2 cytokine production in the airways.⁵⁷ Collectively, these results indicate that caspase-1 promotes allergic asthma development.

7 | ROLE OF NLRP3 INFLAMMASOME IN ASTHMA

The participation of the NLRP3 inflammasome in the development and exacerbation of allergic asthma has been recently demonstrated. In earlier studies, the role of the NLRP3 inflammasome in allergic asthma was rather controversial. Kool et al identified that uric acid crystals promote Th2 cell-driven asthma, and the effects of uric acid crystals on asthma did not require NLRP3 or the IL-1 axis. These results indicate that the NLRP3 inflammasome does not significantly contribute to airway inflammation in mice.⁵⁸ Similarly, Allen et al⁵⁹ found that the NLRP3 inflammasome played only a modest and limited role in an alum-free OVA-induced asthma model and that the NLRP3 inflammasome-related difference did not greatly affect the airway inflammation and symptoms of asthma. However, since 2012, numerous investigations have firmly established the important roles of the NLRP3 inflammasome in asthma. Hirota et al⁶⁰ identified NLRP3 and caspase-1 expression in human airway epithelial bronchus and primary cells, and IL-1 β secretion from these cells has been reported in asthma.⁶¹ Kim et al⁶² developed chlamydia models in *Haemophilus*-infected mice and found that the increased NLRP3, caspase-1, and IL-1 β responses drove steroid-resistant neutrophilic inflammation and airway hyperresponsiveness. Simpson et al showed significantly elevated NLRP3, caspase-1, and IL-1 β gene expression and IL-1 β protein expression in participants with neutrophilic asthma compared with those in healthy controls.⁶³ These authors also found that sputum macrophages and neutrophils expressed NLRP3 and the caspase-1 protein in neutrophilic asthma patients. In severe asthma, the NLRP3 inflammasome expression is significantly increased, and neutrophil-associated NLRP3 inflammasome activation may interact with Th2-driven inflammation.³⁹ Kim et al⁶⁴ found that TiO₂ can lead to NLRP3 inflammasome assembly, which resulted in caspase-1 activation, mature IL-1 β and IL-18 excretion, and airway inflammation induction in asthma. Sebag et al found that mitochondrial Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) mediates ROS production, which stimulates NLRP3 inflammasome activation and promotes inflammation in OVA-induced asthma, whereas MCC950 (an NLRP3 inhibitor) blocked the Mt-CaMKII-mediated effects.⁶⁵ Using

TABLE 1 NLRP3 inflammasome involved in allergic diseases

Disease	Factors	Function	Model	References
Allergic asthma	IL-1 β	Elevated IL-1 β in BALF, sputum, and serum indicates that inflammation exacerbated asthma airway inflammation	Humans	38
				39, 40, 61
		Increased expression of IL-1 β in bronchial epithelium, IL-1R antagonist attenuated asthma airway inflammation	Mice	41,42
		Genetic disruption of the IL-1 signalling pathway reduced allergic responses		47
	IL-18	Overexpression of IL-1 β induced allergic immune responses, inflammation and tissue remodelling		43
		Elevated IL-18 in the BALF, plasma, serum, lung tissue, sputum, and airway biopsies of asthmatic patients	Humans	48
	Caspase-1	Elevated IL-18 promotes inflammation by enhancing antigen-induced eosinophil recruitment into the airway	Mice	49–51
				55
	NLRP3	Increased caspase-1 in serum, biopsies of airway epithelial bronchus, and primary cells	Humans	56
				60
	NLRP3	Inhibition of caspase-1 reduced inflammatory cell number and Th2 cytokine production	Mice	57
		Expression of NLRP3 in airway epithelial, sputum macrophages and neutrophils	Humans	39, 60
				63
		Significantly elevated NLRP3, caspase-1, and IL-1 β gene expression in neutrophilic asthma patients		60
		Increased NLRP3 drove inflammation and airway hyperresponsiveness	Mice	62,65
		TiO $_2$ and CaMKII stimulate NLRP3 inflammasome activation to induce airway inflammation		64
		NLRP3 knockout decreased IL-1 production and airway inflammation		60
Allergic dermatitis	IL-1 β			66
		Application of a specific NLRP3 inflammasome inhibitor completely inhibited HDM-induced AHR and attenuated steroid-resistant asthma		39, 62
	IL-1 β	Elevated IL-1 β production in biopsies of monocytes and primary keratinocytes	Humans	72
		IL-1 β production induced by Ni $^{2+}$ recruit Langerhans cells and lymphocytes to promote skin inflammation	Mice	73
	IL-18	IL-18 increase can discriminate AD	Humans	79
		Overexpressing caspase-1 increased IL-1 β and IL-18 expression in keratinocytes	Mice	81
	Caspase-1	Caspase-1 is activated in human mast cells; caspase-1 activation-regulated IL-1 β and IL-18 production by keratinocytes	Humans	72, 133
		Caspase-1 inhibition by andrographolide attenuated clinical symptoms	Mice	81, 133
	NLRP3	Overexpression of caspase-1 promoted recalcitrant dermatitis		
		NLRP3 is expressed in human keratinocytes	Humans	77
		HDM stimulated NLRP3 inflammasome activation and induced NLRP3 inflammasome-dependent release of IL-1 β and IL-18 from keratinocytes		72
		Chromium (VI) compounds stimulated NLRP3 inflammasome activation to promote IL-1 β secretion in human monocytes and primary human keratinocytes		84
		NLRP3-deficient mice demonstrated an impaired CHS response	Mice	75, 77
		The absence of NLRP3 abolished monobenzone-induced CHS		83
		NLRP3 inflammasome inhibitor reduced skin inflammation		85
Allergic rhinitis	IL-1 β	Increased in plasma, serum, and mast cells of AR patients	Humans	93, 95
		Increased IL-1 β and neutrophil recruitment in grass pollen-sensitive patients		92
		Targeted to attenuate allergic symptoms	Pig	91
		IL-1 β overexpression induced AR inflammation	Mice	94, 96–98
	IL-18	Aberrantly increased in AR patients	Humans	99
				100

(Continues)

TABLE 1 (Continued)

Disease	Factors	Function	Model	References
	Caspase-1	Increased IL-18 concentration in lung lavage fluid	Mice	101
		Increased expression in the mast cells of AR patients	Humans	95
		Attenuation of symptoms in sputum and nasal mucosa tissue after caspase-1 inhibition	Mice	95–98
	NLRP3	Increased NALP3 in the nasal mucosa and nasal polyps of chronic sinusitis patients; local steroid treatment reduced NLRP3 expression in polyposis	Humans	102
		Increased NLRP3 expression in nasal mucosa epithelium in patients with AR		103
		Targeted inhibition of NLRP3 by microRNA-133b strongly attenuated pathological alterations in the nasal mucosa of mice with AR	Mice	104
Allergic conjunctivitis	IL-1 β	Elevated expression in corneal epithelial cells and macrophages	Mice	107, 108, 111
		Significantly increased in AC mice		112–114
		IL-1 β inhibitor reduced symptoms		
		IL-1 β treatment increased VEGF production in cultured conjunctival fibroblasts		

NLRP3-deficient mice, Besnard AG showed that allergic airway inflammation in OVA-induced asthma depends on NLRP3 inflammasome activation, which leads to IL-1 β production and Th2 inflammatory response induction.⁴⁵ The comparison of Nlrp3(-/-) mice group and wild-type mice group under the exposure of particulate matter showed the NLRP3 inflammasome induced IL-1 β production and airway inflammation in the lungs.⁶⁰ Ritter et al⁶⁶ found that airway inflammation and IL-1 β expression in Nlrp3-/- mice were dramatically reduced compared with those in wild-type mice in a model of OVA-induced allergic asthma. Furthermore, the NLRP3-dependent asthma response has been extended to Th17 cells (IL-17 and IL-22), establishing an NLRP3–IL-1–Th17 axis⁶⁷ in which both IL-17 and IL-22 may play dual roles in this response.^{68,69} Importantly, the application of specific NLRP3 inflammasome inhibitors that reduce IL-1 β and Th2 cytokines completely inhibited HDM-induced AHR and attenuated steroid-resistant asthma in a mouse model.^{39,62} Taken together, the above data suggest that NLRP3 inflammasome activation in asthmatic airways and the targeted inhibition of the NLRP3 inflammasome may be therapeutic options for asthma patients. However, the data obtained from these experiments must be replicated with specific NLRP3 inhibitors or gene therapy in animals from different species. The authors suggest that clinical trials investigating specific NLRP3 inhibitors should be carefully considered to further confirm the therapeutic effect on allergic asthma. Altogether, these works could deepen our understanding of NLRP3 in asthma.

8 | ROLE OF THE NLRP3 INFLAMMASOME, IL-1 β , AND IL-18 IN ALLERGIC DERMATITIS

Allergic dermatitis mainly includes allergic contact dermatitis (ACD) and atopic dermatitis. ACD is a common and significant environmental and economic health threat.⁷⁰ Over 2800 chemical compounds have been identified to potentially cause ACD.⁷¹ ACD can occur if susceptible individuals are re-exposed to the same allergen after their first encounter with the allergen. Atopic dermatitis is a chronic

inflammatory skin disorder.⁷² The clinical manifestation of allergic dermatitis typically includes skin irritation, itching, rash, skin peeling, and lesions.⁷³ Skin allergic reactions are typically triggered by allergen complexes that penetrate the skin stratum corneum barrier.⁷⁴

9 | ROLE OF IL-1 β AND IL-18 IN ALLERGIC DERMATITIS

Evidence suggests that NLRP3 inflammasome-related IL-1 β , IL-18, and caspase-1 are involved in skin inflammation.^{75,76} Exposure to contact sensitizers (CS) can cause an immune response called contact hypersensitivity (CHS) in the skin, and during this process, the efficient priming of adaptive immunity is controlled by the concomitant activation of the innate immune system, such as the activation of IL-1 β /IL-18.^{77,78} Corsini et al⁷⁹ found a specific dose-related increase in IL-18 following stimulation with CS that can help discriminate CS from other relevant irritants and low molecular weight respiratory allergens. Kopfnagel et al obtained biopsies from allergic dermatitis patients and by performing an ELISA, detected elevated IL-1 β release. Meanwhile, the increased IL-1 β level was found to be double-stranded B DNA complex dose-dependent and was reduced in the presence of a caspase-1 inhibitor.⁸⁰ Li et al reported that the skin irritant Ni²⁺ could induce IL-1 β production to recruit Langerhans cells and lymphocytes, thus promoting skin inflammation.^{73,77} Yamanaka et al⁸¹ found that overexpressing caspase-1 led to elevated levels of mature IL-1 β and IL-18 in mice keratinocytes that spontaneously developed recalcitrant dermatitis and skin ulcers.

10 | NLRP3 INFLAMMASOME IN ALLERGIC DERMATITIS

The role of the NLRP3 inflammasome in allergic diseases has been gradually clarified. The presence of NLRP3 in keratinocytes form a

TABLE 2 Site of action on the different components and/or assembly of NLRP3 inflammasome

Signal	Component	Site	NLRP3 is mediated by extracellular and/or intracellular pathways
K ⁺ ATP ROS	NLRP3	LLRs	The serine/threonine-protein kinase Nek7 senses the K ⁺ efflux and bound NLRP3 at LLRs (the leucine-rich repeat domain) allowing its activation.
	ASC	PYD	NLRP3 is marked by an N-terminal PYD (pyrin domain) which allows NLRP3 to recruit ASC (inflammasome adaptor protein apoptosis-associated speck-like protein containing CARD) through a homotypic pyrin domain interactions, PYD-PYD, to induce the aggregation of ASC into a large protein speck; thus, facilitating the recruitment of procaspase-1 to form NLRP3 inflammasome complexes. ASC interacts with NLRP3 through its PYD. The tyrosine-protein kinase BTK also binds NLRP3 and apoptosis-associated speck-like protein containing a CARD (ASC). The tyrosine-protein kinase BTK also binds NLRP3 and CARD at PYD.
	Caspase-1	CARD	Caspase-1 interacts with ASC through its CARD (cysteiny aspartate-specific proteinase /caspase recruitment domain). The active NLRP3 oligomerizes, forming a circular structure that functions as a platform for the polymerization of ASC into filaments, which in turn work as a central core from which caspase-1 filaments branch, presenting as a star-like structure, promotes self-cleavage and activation of caspase-1.

first line of defence by rapidly sensing invading pathogens, which triggers innate immune responses by activating the NLRP3 inflammasome and secreting IL-1 β and IL-18.⁸² Sutterwala et al⁷⁵ showed that in a trinitrophenyl chloride-induced CHS model, NLRP3 and ASC-deficient mice have an impaired CHS response compared with wild-type mice. Based on an analysis of allergic disease patients with inflammatory skin lesions, Watanabe et al concluded that NLRP3 may be responsible for CS-mediated IL-1 β activation. Moreover, NLRP3 deficiency significantly attenuated CHS. Based on the above results, the authors concluded that the NLRP3 inflammasome is a key regulator of innate immunity in CHS.⁷⁷ Furthermore, in an atopic dermatitis model, Dai et al found that HDM stimulated NLRP3 inflammasome assembly to recruit ASC, caspase-1, and NLRP3 to the perinuclear region and induced the NLRP3 inflammasome-dependent release of IL-1 β and IL-18 from keratinocytes. These findings demonstrate that the NLRP3 inflammasome plays a key role in the pathogenesis of atopic dermatitis.⁷² Recently, van den Boorn et al⁸³ reported that monobenzone (a pro-hapten) stimulated NLRP3 inflammasome activation to induce adaptive NK cell memory and CHS, whereas the absence of the NLRP3 inflammasome, the adaptor protein ASC or interleukin-18 (IL-18) abolished monobenzone-induced CHS. In 2017, Adam et al⁸⁴ demonstrated that allergy-inducing chromium (VI) compounds potently stimulated NLRP3 inflammasome activation, which processes and secretes IL-1 β , in human monocytes, murine dendritic cells, and primary human keratinocytes. Furthermore, Primiano et al⁸⁵ reported that treatment with specific NLRP3 inflammasome inhibitors reduced skin inflammation induced by imiquimod cream.

The above studies indicate that the NLRP3 inflammasome components or the downstream activated cytokines play important roles in allergic dermatitis and that targeting the NLRP3 inflammasome with small molecule inhibitors may help treat allergic dermatitis. However, to further confirm whether NLRP3 is a promising target for the treatment of allergic diseases, more studies investigating the effects of specific NLRP3 inhibitors or gene therapy should be carried out in various animal models. Furthermore, clinical studies investigating targeted NLRP3 treatment for allergic diseases should be considered in the future.

11 | ROLE OF THE NLRP3 INFLAMMASOME, IL-1 β AND IL-18 IN ALLERGIC RHINITIS (AR)

Allergic rhinitis is an allergic disease that occurs in the nasal mucosa. The clinical manifestations of AR include sneezing, thin or watery nasal discharge, congestion, and nasal itching. The average incidence of AR is between 10%–25% world-wide and 20%–30% in most Westernized countries.⁸⁶ During a World Health Organization workshop titled Allergic Rhinitis and its Impact on Asthma (ARIA), AR was first reclassified by the following levels: mild/moderate-severe and intermittent/persistent.⁸⁷ This classification reveals that clarifying the pathogenesis of AR is essential for identifying new effective treatment methods. According to reports, the major allergen in AR in China is HDM, which is responsible for up to 59% of AR cases.⁸⁸ Jacquet et al found that HDM could contain lipopolysaccharide (LPS) and β -glucan from microorganisms, which can activate PRRs and then form the inflammasome to induce Th2 cell polarization.⁸⁹ Subsequent research has also reported that HDM can promote dendritic cells, epithelial cells, and macrophages to release ATP and activate inflammasomes.⁹⁰

12 | ROLE OF IL-1 β AND IL-18 IN AR

Increasing evidence suggests that IL-1 is critically involved in the development of AR. Bachert et al and Guo-Zhu et al found that IL-1 β blockade could be a promising strategy for preventing and treating AR.⁹¹ Another study conducted by Leaker et al⁹² analysed whole-genome expression profiles of AR patients and observed type 2 inflammation upregulation involving IL-1 β . Bocşan et al⁹³ measured plasma IL-1 β levels in patients with persistent AR after H1 antihistamine treatment and found that H1 antihistamines reduced plasma the IL-1 β levels and symptoms of AR. In an OVA mouse model of induced AR, researchers have shown that the serum concentrations of IL-1 β and the nasal septum levels of caspase-1 in the OVA group were significantly higher than those in the control group. Moreover, Gami-hyunggyeyeongyotang, which is a polyherbal medicine derived

from an oriental prescription traditionally used for the treatment of allergic diseases, can attenuate allergic inflammation in AR by suppressing IL-1 β and caspase-1 expression via the inflammatory pathway in human mast cells.⁹⁴ Several other research studies have revealed that the levels of IL-1 β and caspase-1 in the serum or nasal mucosa tissue were increased in the OVA-induced AR mice compared with those in the control mice and that the administration of anti-allergic drugs inhibited IL-1 β and caspase-1 expression and attenuated the allergic symptoms.^{95–98}

IL-18 is also considered an important regulator in AR. One study found that the serum IL-18 levels were significantly higher in children with AR.⁹⁹ Verhaeghe et al¹⁰⁰ reported elevated IL-18 concentrations in nasal secretions from seasonal AR patients and persistent AR patients, indicating the relevance of IL-18 for AR. In a mouse model of AR, Kim et al¹⁰¹ found that the IL-18 concentrations were increased in lung lavage fluid in the OVA-induced model group, but the increased IL-18 concentration was decreased after a steroid treatment. These findings suggest that IL-18 is involved in AR pathogenesis.

13 | ROLE OF NLRP3 INFLAMMASOME IN AR

Mansson et al observed that NALP3 is over-expressed in nasal mucosa from patients with chronic sinusitis and nasal polyps compared with that in normal nasal mucosa and that local steroid treatment reduced the NLRP3 expression in polyposis, highlighting the potential role of NLRP3 in chronic rhinitis.¹⁰² Bogefors et al¹⁰³ found that NLRP3 expression in the nasal mucosa epithelium was significantly increased in patients with AR but decreased as the symptoms were controlled. Moreover, the targeted inhibition of NLRP3 by microRNA-133b reduced the caspase-1, ASC, IL-18 and IL-1 expression levels and strongly attenuated the pathological alterations and eosinophil and mast cell infiltration in nasal mucosa from mice with AR.¹⁰⁴

In summary, the current evidence suggests that the NLRP3 inflammasome and its related cytokines promote the development of AR. However, an improved understanding of the involvement of the NLRP3 inflammasome in AR is greatly needed. First, NLRP3 knocked-out animal models should be used to further elucidate the role and mechanisms of the NLRP3 inflammasome in AR. Second, more data are needed regarding the application of specific NLRP3 inflammasome inhibitors in various animal models in the future.

14 | ROLE OF IL-1B IN ALLERGIC CONJUNCTIVITIS (AC)

Allergic conjunctivitis is a common ocular inflammatory disease that can present as mild transient inflammation. This disease encompasses a diversity of pathological conditions and fundamental immunopathological mechanisms. Therefore, AC can be subdivided into seasonal and perennial allergic conjunctivitis.¹⁰⁵ Previous data

suggest that 15%–40% of the population world-wide are affected by AC.¹⁰⁶ AC is induced by a hypersensitivity response after exposure to some allergens, such as pollen and HDM.

Studies have shown that IL-1/IL-1R is important for mast cell activation and mast cell-mediated AC.^{107,108} Fukuda reported that IL-1 released from necrotic corneal epithelial cells cooperates with Th2 cytokines to induce chemokine (C-C motif) ligand 11 production and vascular cell adhesion molecule 1 expression in corneal fibroblasts and may, therefore, play an important role in ocular allergic diseases.¹⁰⁹ Abu et al demonstrated that conjunctival epithelial cells from trachomatous conjunctivitis patients expressed IL-1 α and IL-1 β . These authors also detected the cytoplasmic expression of IL-1 α and IL-1 β in macrophages, and these cytokines had the potential to influence remodelling and fibrosis in trachomatous conjunctivitis.¹¹⁰ Furthermore, Goldstein et al¹¹¹ found that EBI-005, which is an IL-1 β inhibitor, has significant biological activity to attenuate symptoms in AC patients. In an OVA-induced guinea-pig model of AC, the mRNA levels of IL-1 β in the model group were much higher than those in the control group; however, a dose-dependent reduction in IL-1 β mRNA levels was observed after the administration of Mapracorat (a selective glucocorticoid receptor agonist). These results confirm that IL-1 β may represent a useful marker for monitoring the anti-allergic efficacy of drugs in AC.¹¹² In another LPS-induced conjunctivitis rat model, the IL-1 β levels were significantly increased. Chen et al found that following treatment with carvedilol, which is a novel third generation β -blocker, the expression of IL-1 β was reduced compared to that in the model group.¹¹³ Asano-Kato et al¹¹⁴ found that the VEGF concentration in cultured conjunctival fibroblasts was significantly increased following incubation with IL-1 β . These findings indicate that IL-1 β from allergic inflammatory cells plays an important role in the development of AC. The authors commented that further research should be performed to directly elucidate NLRP3 expression in patients and that NLRP3 knockout mice models should be used to better understand the role of NLRP3 in AC. Moreover, the application of specific NLRP3 inflammasome inhibitors in animal experiments may help clarify their therapeutic effects in AC.

15 | ROLE OF NLRP3 INFLAMMASOME IN OTHER ALLERGIC DISEASES

NLRP3 is involved in the pathological mechanisms of other allergic diseases. Anaphylactic stimuli activate the NLRP3 inflammasome and induce IL-1 β secretion, which plays an important role in triggering and sustaining allergic inflammation in mast cells. Mast cells play detrimental roles in the pathophysiology and mortality of anaphylaxis.¹¹⁵ In peanut-allergic mice, peanut allergy induces uric acid, which enhances the NLRP3 inflammasome via a PI3K signalling pathway and plays a critical role in the induction of peanut-allergic sensitization.¹¹⁶ Abacavir, which is an HIV-1 reverse transcriptase inhibitor, often induces severe delayed-type drug hypersensitivity that potently triggers IL-1 β release. Thus, abacavir was identified as a specific NLRP3 activator.¹¹⁷ Collectively, increasing evidence

indicates that the NLRP3 inflammasome is involved in these allergic diseases. However, more studies, including studies using NLRP3 knockout mouse models and specific NLRP3 inflammasome inhibitors, are needed to further elucidate the role and mechanisms of the NLRP3 inflammasome in these allergic diseases.

16 | SUMMARY

Our understanding of the mechanism of inflammasome-caspase activation has vastly increased in recent years. In addition, studies investigating the effect of different inflammasome components and their downstream factors in allergic disorders are accumulating. Thus, targeting these components, such as NLRP3 or ASCs, might be more effective than targeting caspases or cytokines. Although much progress has been made towards elucidating the role of NLRP3 inflammasomes in inflammatory pathologies, our knowledge of the activation and regulation of the NLRP3 inflammasome in allergies remain limited. Hence, a deeper understanding of the inflammasome complex could be advantageous for translating these findings into therapies in clinical practice. For example, future studies should aim to better define the types of cells in which the NLRP3 inflammasome is activated in allergic disease models and dissect the contributions of IL-1 β and IL-18 to these pathologies. Detailing the specific mechanisms by which NLRP3 regulates adaptive immunity may considerably contribute to exploiting more effective approaches for controlling T-cell-mediated autoimmune diseases and developing adjuvants for vaccinations in the future.

Several specific inhibitors, such as MCC950, CY-09, arglabin, and glyburide, have been recently developed or identified to target NLRP3 inflammasome inhibition.^{39,62,118–121} The application of these specific NLRP3 inflammasome inhibitors has demonstrated therapeutic effects in various inflammatory disease mouse models, including models of myocardial infarction,¹¹⁸ fulminant hepatitis,¹²² steatohepatitis,¹²³ lupus nephritis,¹²⁴ atherosclerosis,¹²⁵ Alzheimer's disease,¹²⁶ brain injury,^{127,128} inflammatory bowel diseases,¹²⁹ acute colitis,¹³⁰ and carcinoma.^{131,132} In allergic diseases, the application of MCC950 reduces skin and airway inflammation in mouse models of allergic dermatitis and asthma.⁸⁵ More recently, 2 studies have shown that the targeted inhibition of NLRP3 inflammasomes with a specific inhibitor decreased IL-1 β and TH2 cytokines and inhibited HDM-induced AHR and steroid-resistant asthma in a mouse model.^{39,62} These studies further suggest the potential of targeting NLRP3 inflammasomes for the treatment of allergic diseases. In summary, we highlighted the accumulating evidence regarding the role of the NLRP3 inflammasome, IL-1 β , and IL-18 in various allergic diseases. In the future, more research focusing on NLRP3 is needed because NLRP3 is a possible promising therapeutic target with wide clinical applications for the treatment of allergic diseases.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Conception and design: W.S.; Drafting and revising of the article: W.S., Y.X., and W.X.; Final approval: W.S.

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